# Exploring $GABA_A$ Receptor Pharmacology: Unveiling Insights with the PQ Toolbox

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$GABA_A$-receptors are among the major neurotransmitter receptors in the mammalian brain and are involved in conditions such as anxiety disorder, epilepsy, and insomnia. The ligand-gated ion channels are composed of five different subunits encoded by 19 different genes. This results in numerous potential subunit combinations, and hence, a highly complex pharmacology. $GABA_A$ receptors are prominent targets for many pharmacologically and clinically important drugs such as benzodiazepines, barbiturates, neuroactive steroids, anesthetics, and anticonvulsants which bind to various binding sites.

Several pyrazoloquinolinone ligands (PQs) with high potency for $GABA_A$ receptors have been reported. These allosteric modulators potently act via a binding site at extracellular α+/β− interfaces. However, this chemotype also tends to interact promiscuously with other binding sites on the receptor, including the benzodiazepine binding site at α+/γ− interfaces and the etomidate binding site (Figure 1). To further complicate matters, previous research has demonstrated that even minor changes in the pharmacophore features of PQs can lead to radical changes in ligand binding properties.

The presented work shows the design and synthesis of novel PQ-ligands that aim to address persistent challenges such as binding site selectivity and receptor subtype specificity. Furthermore, isotope-labeled PQs have been developed to unravel the complex structure-activity relationships and decipher the intricate code of $GABA_A$ receptor pharmacology.

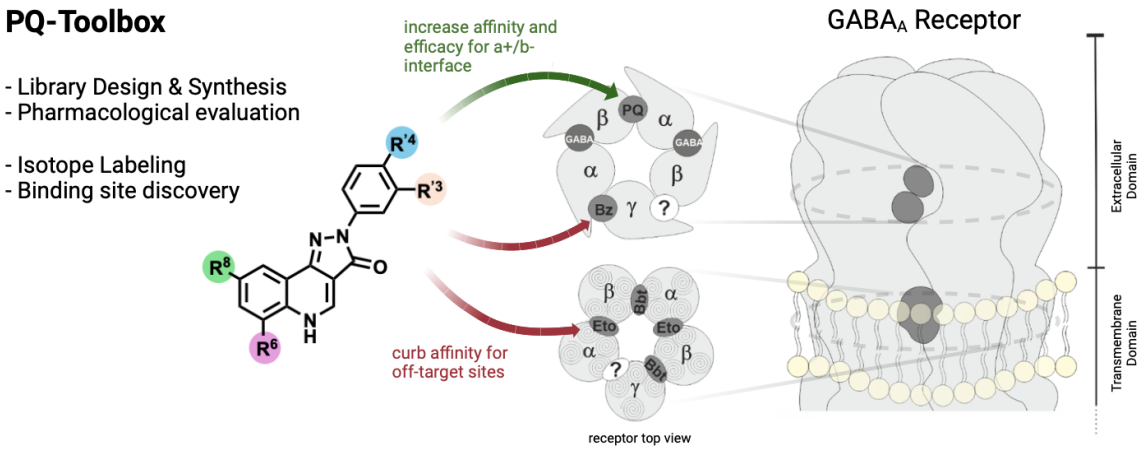


*Figure 1: Structure of pyrazoloquinolinones and their binding sites at the extracellular (top) and transmembrane domain (bottom). Depicted binding sites: pyrazoloquinolinones (PQ), benzodiazepines (BZ), Etomidate (Eto), Barbiturates (Bbt).*